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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/653,114	05/24/96	FALCK-PEDERSEN	E	19603/233(CR

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/653,114	Falck-Pedersen
Examiner	**Group Art Unit**
Richard Schnizer	1632

☒ Responsive to communication(s) filed on *Jun 25, 1998*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-4, 7-11, 13-15, and 17* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 7-11, 13-15, and 17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

The request filed on 6/25/98 (paper #22) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/653114 is acceptable and a CPA has been established. Claims 5, 6, 12, and 16 have been canceled. An action on the CPA follows.

Claims 1-4, 7-11, 13-15, and 17 remain pending in the instant application.

The Declaration filed on 6/25/98 under CFR 1.132 (Paper #23; Falck-Pedersen Declaration) has been considered as indicated below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for host cells *in vitro*, does not reasonably provide enablement for host cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 14 and 15 read on methods of producing selected proteins in host cells. Useful host cells are defined as including any mammalian cell in which the recombinant adenovirus and/or

vector are capable of uptake and expression. This comprises both cultured cells and multicellular mammalian organisms. While techniques for obtaining stable gene expression in cultured cells are discussed, no correponding techniques for whole animals are mentioned. Also, techniques for delivering the recombinant vector or adenovirus to appropriate mammalian tissues are not discussed. Given the unpredictable nature of the *in vivo* environment, in the absence of such guidance the artisan would have been required to have exercised undue experimentation to practice the invention *in vivo*. Inclusion of the term "*in vitro*" in claims 14 and 15 would be remedial.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 4, 7, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because "said gene" in line 4 of the claim lacks antecedent basis. Applicant claims "at least one insertion site for cloning a selected heterologous gene" (lines 2 and 3 of the claim). The insertion site, rather than the heterologous gene, is explicitly claimed. The heterologous gene cannot serve as an antecedent. Similarly, the phrases "the left end" in line 4 of the claim, and "the adenovirus-5 genome" in line 5 lack antecedent basis.

Claim 3 is vague and indefinite because "the mouse cytomegalovirus promotor" in line 2 lacks antecedent basis.

Claim 4 is vague and indefinite because "the 3' processing site from the mouse β-globin transcription unit" lacks antecedent basis. The identity of the processing site is unclear. The processing site may be located 3' to the gene, or it may be the 3'-most signal of several polyadenylation signals. If there is only a single polyadenylation signal in the mouse β-globin transcription unit, then it need not be referred to as "3'". If there is more than one signal, then the claim should recite precisely which signal is intended for use.

Claim 7 refers to Figures 1a and 1b, which are schematic representations of a plasmid vector and a recombinant adenovirus, respectively. Such representations are, by their nature, indefinite and cannot be claimed. It is preferable to state such claims as comprising a nucleotide sequence with reference to a specific Seq. Id (as in claim 8).

Claim 14 is vague and indefinite because "said heterologous DNA" in line 4 of the claim lacks antecedent basis. Claim 14 is indirectly dependent on claim 10 which recites a "heterologous gene" specifically, rather than the more general "heterologous DNA".

Claims 14 and 15 are vague and indefinite because they are incomplete. The claimed processes are drawn to methods of producing proteins, however the only operational step recited

is "culturing" a host. Inclusion of expression and recovery steps would complete the claimed process.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Kirshenbaum *et al.*, Quantin et al., or Stratford-Perricaudet *et al.;* in view of Huang *et al.*, Choi *et al.*, Keating *et al.*, and KabiGen.

The invention is an expression vector comprising adenoviral replication and packaging elements, a promoter, a splice junction, at least one gene insertion site, a polyadenylation signal, and adenoviral sequences suitable for homologous recombination. Plasmid and infectious adenoviral forms of the vector are claimed, as is a method of producing the adenoviral form. A form of the vector containing a gene to be expressed is claimed, as is a unicellular host transformed with the vector. Methods of producing a selected protein by culturing infected or transformed hosts with the claimed vectors are also claimed.

Kirshenbaum *et al.* disclose a plasmid vector having Ad5 sequences which, when cotransfected with a mutant Ad5 construct into 293 cells, can recombine to produce a replication-incompetent virus containing the plasmid expression cassette (entire document, *e.g.* Methods). The replication cassette contains the human CMV promoter, the lacZ gene and the SV40

polyadenylation signal sequence. Within the plasmid, the expression cassette is flanked by Ad5 sequences that read on the left end packaging and replication sequences and homologous recombination sequences recited in claim 1. Kirshenbaum *et al.* also disclose transfected host cells producing β-galactosidase. Quantin *et al.* and Stratford-Perricaudet *et al.* each disclose similar products and methods, only different promoter and polyadenylation sequences are used in the expression cassette. None of the above three references discloses an expression cassette containing a splice site between the promoter and the gene to be expressed, nor do they disclose the use of the murine CMV early promoter and murine β-globin polyadenylation signal sequences. Huang *et al.* teach that including a splice site in the 5' untranslated portion of the gene to be expressed resulted in a much higher level of gene expression in several cell lines, including 293 (entire document, e.g. Fig. 2). Furthermore, Choi *et al.* (abstract) teach that incorporation of a generic intron between the promoter and the gene of interest causes 5- to 300-fold increases in transgene expression in mice. Keating *et al.* teach that the murine immediate early CMV promoter produces a high level of gene expression in transfected cells (Table 1, Fig. 1). The KabiGen disclosure teaches that polyadenylation sequences from rodent β-globin genes yield efficient RNA processing in transfected cells (p5, lines 10-15). KabiGen also discloses vectors which contain additional cloning sites for insertion of additional genes (Figures).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the expression cassette of Kirshenbaum *et al.*, Quantin *et al.*, or Stratford-Perricaudet *et al.*, by including the splice site of either Huang *et al.* or Choi *et al.*, the murine CMV promoter of Keating *et al.*, and the murine β-globin polyadenylation sequence suggested by

KabiGen. One skilled in the art would have been motivated to use these components in the expression cassette, given their recognized value for promoting high level gene expression and given the expectation that each component would continue to function in its known and expected manner. The specific adenoviral sequence included for recombination is a result-effective variable which would have been routinely optimized by one of ordinary skill in the art. Thus the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made.

It is noted that Applicant has ammended claim 1 to recite "a portion of the adenovirus-5 genome which is suitable for homologous recombination", however no distinguishing structural features appear to be required to meet this intended use limitation.

Responses to Amendments and Arguments

The declaration under 37 CFR 1.132 filed June 25, 1998 is insufficient to overcome the rejection of claims 1-17 based upon Kirshenbaum *et al.*, Quantin *et al.*, or Stratford-Perricaudet *et al.*, in view of Huang *et al.*, Choi *et al.*, Keating *et al.*, and KabiGen as set forth in the last Office action because:

Applicant argues that none of Kirshenbaum, Quantin, or Stratford-Perricaudet teaches a splice site, and that Huang does not teach a vector capable of forming a recombinant retrovirus. These references were not relied upon for such teachings.

Applicant argues that Huang *et al.* is irrelevant to recombinant adenoviral expression systems, and that there is no basis for concluding that splice signals included in adenoviral expression vectors would function similarly to those included in plasmid expression vectors. The

relevance of Huang is precisely that the expression of a heterologous gene can be enhanced by the inclusion of splice donor and acceptor sites. This phenomenon has been demonstrated on plasmid (Huang *et al.*), viral (Buchman and Berg), and chromosomal (Choi *et al.*) expression platforms. It had not been demonstrated on an adenoviral expression vector prior to Applicant's invention. However, such intron-dependent increases in gene expression are thought to be due to posttranscriptional events rather than increased frequency of transcription initiation (Huang *et al.*), or to other events dependent on the structure of the DNA template. The argument that one of ordinary skill in the art would not reasonably expect a similar increase in expression from the adenoviral expression platform is therefore unconvincing.

Applicant argues that there is no reason to expect that the mouse CMV promoter will achieve a "higher" level of expression in the context of a recombinant adenovirus platform. It is unclear what the CMV promoter is being compared to in this argument (Paper 22, pg. 6). Keating *et al.* was cited by the examiner as evidence that the CMV promoter functions well ("produces a high level of gene expression") in transfected cells. Any argument that the CMV promoter will not function well in an adenoviral context is rebutted in view of Kirshenbaum *et al.*, who infected ventricular myocytes with a recombinant adenovirus which expressed the *lac Z* gene under the control of a human CMV promoter. Further, Ishibashi *et al.* used a mouse CMV promoter in their recombinant adenoviral vector to drive expression of the human low density lipoprotein (LDL) receptor in transgenic mice engineered to lack the murine LDL receptor. Expression of the human receptor in infected mice was sufficient to complement the genetic

defect. Finally, Applicant has provided no evidence to support the proposition that either the CMV promoter or a splice junction will not function properly in an adenoviral context.

Applicant presents results which demonstrate that the insertion of a splice junction improves gene expression. This result is not unexpected. As stated previously, Huang *et al.* teach that inclusion of a splice junction increases gene expression.

Applicant argues that the vector pAdCMVCATgD achieves better expression than the vectors of Quantin, Stratford-Perricaudet, or Kirshenbaum. This has not been demonstrated because the actual vectors of Quantin, Stratford-Perricaudet, and Kirshenbaum were not used for the comparison performed in the Falck-Pedersen Declaration. In any case, demonstration that these vectors are inferior in terms of gene expression would not support a claim of unexpected results precisely because these vectors do not contain splice junctions (see Huang *et al.*).

Applicant presents data which show that, under the conditions described in the Falck-Pedersen Declaration, gene expression from pAdCMVCATgD is greater than that from the vector of Huang (which contains a different promoter, a different intron, and a different polyadenylation signal). This asserted unexpected result is not commensurate with the scope of the claims. It was well known to those of ordinary skill in the art at the time the invention was made that the performance of a promoter is dependent on the cell type (which determines the transcription factors present) in which it is located. In some cells, the SV-40 promoter will outperform the CMV promoter (Li *et al.* , abstract), in other cells the reverse is true. Furthermore, factors such as the identity of the splice junction used (Choi *et al.*, abstract), and the identity and placement of polyadenylation signals (Pfarr *et al.*, abstract) will also influence the effectiveness of gene

expression. The claims as stated encompass all mammalian cell types capable of uptake and expression of the claimed vectors. The claimed vectors encompass all the possible combinations of all the natural or synthetic promoters, splice donor sites, splice acceptor sites, and polyadenylation sites existing or yet to exist. It is clear that each and every one of the possible combinations of these various elements will not perform better than the vector of Huang in all useful cells. For example, in the Falck-Pedersen Declaration, neither pMLSISCATL3 nor pMLSISCATgD outperform the vector of Huang.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-308-8990. The examiner can normally be reached Monday-Friday from 7:30 to 4:00 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached at 703-308-2801. The FAX phone number for art unit 1632 is 703-308-0294.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

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